page 1 of the application to replace the original statement of the continuity data with a new statement that is consistent with the priority data contained in the Declaration filed herein which correctly identifies the parent application as follows: "This application claims benefit from provisional application 60/008,316, filed December 7, 1995, and is a continuation of application Serial No. 08/651,568, filed May 22, 1996, now issued as U.S. Patent 5,939,250." In view of the amendment of the statement of priority in the application, Applicant respectfully submits that any confusion regarding the priority documents for this application is now overcome.

The Information Disclosure Statement

Applicant traverses the Examiner's assertion in the Office Action that the Information Disclosure Statement filed August 17, 1999 herein fails to comply with 37 CFR 1.98(a)(1). Applicant disagrees with the Examiner's statement that the Information Disclosure Statement included two pages of PTO-1449 that are copies of the IDS filed in the parent case and four pages of form PTO-892 from the parent file. Applicant respectfully submits that the Information Disclosure Statement was accompanied by a single sheet of PTO Form 1449, listing two references, as shown a copy of the return postcard attached. Furthermore, the pages from the parent application referenced by the Examiner were submitted with the transmittal papers for the present application for the convenience of the Examiner in carrying out the instructions contained in MPEP § 609, which states in part:

> ...The Examiner will consider information which has been considered by the Office in a parent application when examining ... (C) a continuation-in-part application (see MPEP §201.06(b)) filed under 37 C.F.R. 1.53(b), and a list of the information need not be submitted in the continuation, divisional, or continuation-in-part application unless applicant desires the information to be printed on the patent.

Thus, Applicant respectfully submits that the Information Disclosure Statement filed herein (which was accompanied by two references and a PTO Form 1449 listing the two references) meets all requirements of 37 C.F.R. §1.98(a)(1). In addition, Applicant requests consideration in

the present application in accordance with MPEP 609 of the references considered by the Office in the parent application 08/651,568, now issued as U.S. Patent 5,939,250. If for any reason the references considered in the parent application are unavailable to the Examiner, Applicant will provide additional copies of the references for consideration.

The Objection to the Specification

Applicant traverses the objection to the Specification for use of the term "shuffling" in claims 21, 23 and 40, which objection was based on the Examiner's assertion that "the original specification and the claims of the parent application allegedly fail to provide proper antecedent basis" for use of the term in the present claims (Office Action page 2). In view of the cancellation of claims 17-40, Applicant submits that the objection to the Specification is now moot. Therefore, Applicant respectfully submits that the objection is without merit and requests reconsideration and withdrawal of the objection to the Specification.

The objection to the claims

Applicant traverses the objection to claims 25 and 31 as having a scope identical to claims 23 and 24, respectively, based on the assertion that "shuffling and "assembly PCR" appear to be identical methods and that oligonucleotide-directed mutagenesis is defined in the specification as site specific mutagenesis at page 13, paragraph 3" (Office Action, pages 2-3).

In view of the cancellation of claims 17-40, Applicant submits that the objection to the Specification is now moot. Therefore, Applicant respectfully submits that the objection is without merit and requests reconsideration and withdrawal of the objection to the claims.

The Rejection under 35 U.S.C. §112, second Paragraph

Applicant respectfully traverses the rejection of claims 17-40 under 35 U.S.C. §112, Second Paragraph, for allegedly being indefinite. In view of the cancellation of claims 17-40, Applicant submits that the rejection of claims 17-40 for allegedly lacking definiteness is now moot. Therefore, Applicant respectfully submits that the objection is without merit and requests reconsideration and withdrawal of the rejection.

The Rejection Under 35 U.S.C. §102(b)

Applicant respectfully traverses the rejection of claims 17-19, 21, 22, 24, 27, 28, 31-36 and 38-40 under 35 U.S.C. §102(b) as allegedly being anticipated by Arnold et al. (U. S. Patent 5,316,935; hereinafter "Arnold"). In view of the cancellation of claims 17-40, Applicant submits that the rejection of the above claims over Arnold is now moot. Therefore, Applicant respectfully requests reconsideration and withdrawal of the rejection over Arnold.

In addition, Applicant respectfully traverses the rejection of claims 17-19, 21-25, 28, 31-36 and 38-40 under 35 U.S.C. §102(b) as allegedly being anticipated by Stemmer et al. (U. S. Patent 5,605,793; hereinafter "Stemmer"). In view of the cancellation of claims 17-40, Applicant submits that the rejection of the above claims over Stemmer is now moot. Therefore, Applicant respectfully requests reconsideration and withdrawal of the rejection over Stemmer.

The Rejection Under 35 U.S.C. §103

Applicant respectfully traverses the rejection of claims 20, 21, 23, 25, 26, 29, 30, 37 and 40 under 35 U.S.C. §103 for allegedly being unpatentable over Stemmer in view of the state of the art as exemplified by Delagrave et al. (*Biotechnol.* 1993, 11:1548-1552), Arkin et al. (*Proc. Natl. Acad. Sci. U.S.A.* 1992, 89:7811-7815), and Stemmer B (Stemmer et al. *Proc. Natl. Acad. Sci. U.S.A.* 1994, 91:10747-10751). "). In view of the cancellation of claims 17-40, Applicant submits that *prima facie* obviousness of claims 20, 21, 25, 26, 29, 30, 37 and 40 has not been established over over Stemmer in view of the state of the art as exemplified by Delagrave et al. (*Biotechnol.* 1993, 11:1548-1552), Arkin et al. (*Proc. Natl. Acad. Sci. U.S.A.* 1992, 89:7811-7815), and Stemmer B (Stemmer et al. *Proc. Natl. Acad. Sci. U.S.A.* 1994, 91:10747-10751). Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

The Double Patenting Rejection

Applicant respectfully traverses the rejection of claims 17-40 as unpatentable under the judicially created doctrine of double patenting over claims 1-12 of U.S. Patent No. 5,939,250. In view of the cancellation of claims 17-40, Applicant submits that the rejection of the above claims over U. S. Patent No. 5,939,250 is now moot. Therefore, Applicant respectfully requests reconsideration and withdrawal of the rejection.

In view of the above amendments and remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect respectfully is requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: 7/26/01

Lisa A. Haile, Ph.D.
Reg. No. 38,347
Attorney for Applicant
Telephone No.: (858) 677-1456
Facsimile No.: (858) 677-1465

GRAY CARY WARE & FREIDENRICH LLP
USPTO Customer Number 28213
4365 Executive Drive, Suite 1600
San Diego, California 92121-218

Attachments:
Exhibit A
Copy of Postcard

Gray Cary\ \6246241.3
104703-159694

EXHIBIT A
Version with Markings to Show Changes Made

In the Specification

At page 1, please delete the first paragraph and substitute the following new paragraph:

-- This application claims benefit from provisional application 60/008,316, filed December 7, 1995, and is a continuation of application Serial No. 08/651,568, filed May 22, 1996, now issued as U.S. Patent 5,939,250. --

At page 6, 2 lines from the bottom, at page 19, line 2, and at page 22, line 6, please add a --®-- symbol after "ZAP".

At page 9, lines 24 and 25, please delete "pBluescript" and substitute therefor -- pBLUESCRIPT®--.

At page 22, line 13, and at page 23, lines 2 and 13, please delete "Biomek" and substitute therefor --BIOMEK®--, and at page 22, line 15, please delete "Dynatech" and substitute therefore --DYNATECH®--.

At page 26, lines 7 and 16, please delete "Qiaquick" and substitute therefore – QIAQUICK®--.

In the Claims

Please cancel claims 17-40 without prejudice.amend claims 17, 32, and 34 as follows:

Please add new claims 41-70 as follows:

--41. (New) A method for obtaining a desired bioactivity or biomolecule, comprising:
a) creating a DNA library comprised of DNA molecules obtained directly from an environmental source;
b) introducing at least one mutation into a DNA molecule from said library to create a mutagenized DNA molecule; and
c) screening for a desired bioactivity or biomolecule containing a mutation.

whereby, if desired, biomolecules can be accessed from uncultivated organisms, and, if desired, improved thru mutagenesis in directed evolution.

42. (New) The method of claim 41, further comprising the step of:
d) expressing the mutagenized molecule of step (b) to create a bioactivity or biomolecule containing a mutation.

43. (New) The method of claim 41, wherein, for step a), the DNA is genomic DNA.

44. (New) The method of claim 43, wherein the genomic DNA is at least 1 kb in size.

45. (New) The method of claim 43, wherein the genomic DNA is at least 5 kb in size.

46. (New) The method of claim 43, wherein the genomic DNA is at least 10

47. (New) The method of claim 43, wherein the genomic DNA is at least 15 kb in size.

48. (New) The method of claim 43, wherein the genomic DNA is at least 20 kb in size.

49. (New) The method of claim 43, wherein the genomic DNA is at least 30 kb in size.

50. (New) The method of claim 43, wherein the genomic DNA is at least 35 kb in size.

51. (New) The method of claim 43, wherein the genomic DNA is at least 45 kb in size.

52. (New) The method of claim 43, wherein the genomic DNA is at least 60 kb in size.

53. (New) The method of claim 43, wherein the genomic DNA is at least 75 kb in size.

54. (New) The method of claim 43, wherein the genomic DNA is at least 150 kb in size.

55. (New) The method of claim 43, wherein the genomic DNA is at least 200 kb in size.

56. (New) The method of claim 41, wherein the DNA comprises at least one gene cluster.

57. (New) The method of claim 41, wherein the DNA encodes a gene cluster involved in production of polyketide synthases.

58. (New) The method of claim 41, wherein the DNA encodes a gene cluster involved in production of polyketides.

59. (New) The method of claim 58, wherein the polyketides are selected from the group consisting of antibiotics, anti-cancer agents, and immunosuppressants.

60. (New) The method of claim 41, wherein the DNA encodes a molecule useful in a veterinary product.

61 (New) The method of claim 41, wherein the DNA encodes at least one operon.

62. (New) The method of claim 41, wherein, for step a), the library is made using a vector.

63. (New) The method of claim 62, wherein the vector is selected from the group consisting of viral particles, baculovirus, phage, plasmids, phagemids, cosmids, fosmids, bacterial artificial chromosomes, and viral DNA.

64. (New) The method of claim 63, wherein the vector includes chromosomal, nonchromosomal or syntheitic DNA.

65. (New) The method of claim63, wherein the vector contains suitable regulatory sequence for effecting expression of at least a portion of the DNA.

66. (New) The method of claim 41, wherein, for step a), where the environmental sample is obtained from a locality selected from the group consisting of artic, antartic, volcanic and tropical locations.

67. (New) The method of claim 64, wherein in the environmental sample is soil, water, permafrost, or plant.

68. (New) The method of claim 41, further comprising:

(c) enriching for a particular organism or organisms of interest.

69. (New) The method of claim 41, wherein the DNA is derived from a plurality of donor organisms.

70. (New) The method of claim 65, wherein step (c) is comprised of hybridization screening.--